



# Epigenetic control of mobile DNA as an interface between experience and genome change

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Mobile DNA in the genome is subject to RNA-targeted epigenetic control. This control regulates the activity of transposons, retrotransposons and genomic proviruses. Many different life history experiences alter the activities of mobile DNA and the expression of genetic loci regulated by nearby insertions. The same experiences induce alterations in epigenetic formatting and lead to trans-generational modifications of genome expression and stability. These observations lead to the hypothesis that epigenetic formatting directed by non-coding RNA provides a molecular interface between life history events and genome alteration.

**Keywords: mutation, evolution, natural genetic engineering, mobile DNA, viruses, mobile genetic elements, non-coding RNA**

## INTRODUCTION

Understanding the functional organization of the genome and its evolutionary history are key goals of modern molecular biology. The task has become more interesting and complex as we learn more the details of cell processes involving the genome. Recent applications of high resolution technologies to genome expression in animals reveal a dynamic four-dimensional interactive control architecture incompatible with prior notions that genomes contain discrete functional segments of DNA (“genes”) (Mercer and Mattick, 2013). This review will focus on the role of epigenetic regulation of viruses and mobile genetic elements as a key interface between the activities of these agents of evolutionary change and inputs from cell and organism life histories. The hypothesis developed as a result of the review is that disruption of epigenetic silencing constitutes a major target for life history activation of cellular functions for genome change. This likely occurs after genome replication, possibly by changes in small non-coding (snc) RNAs, typically on the order of 20–50 nucleotides long.

## MOBILE DNA IS A MAJOR AND FUNCTIONALLY SIGNIFICANT COMPONENT OF GENOMES

One of the major surprises to come from the initial sequencing of the human genome was the high abundance of dispersed mobile repeat elements (Consortium, 2001). Today, we estimate that at least two-thirds of our genomes is composed of mobile DNA (De Koning et al., 2011). The human genome is not exceptional in its high content of mobile DNA (<http://shapiro.bsd.uchicago.edu/TableII.1.shtml>).

We increasingly recognize that viruses contribute to cell genomes (Kokosar and Kordis, 2013). They provide sequences for non-coding ncRNAs (Frias-Lasserre, 2012), sites for transcriptional control (Peaston et al., 2004; Dunn et al., 2005; Maksakova et al., 2006; Conley et al., 2008), and elements important in epigenetic regulation (Brunmeir et al., 2010; Conley and Jordan, 2012).

Similar transcriptional and epigenetic regulatory contributions are made by mobile genetic elements (<http://shapiro.bsd.uchicago.edu/Table5C-1.MobileElementsFoundtoBeExaptedAscis-RegulatoryControlSitesinAnimals.html>) (Youngson et al., 2005; Kinoshita et al., 2007; Suzuki et al., 2007; Fujimoto et al., 2008; Gehring et al., 2009; Pask et al., 2009; Nakayashiki, 2011).

Mobile DNA is a major source of novel coding information. One mechanism is the process known as “exonization,” when splice signals are utilized in newly inserted DNA segments ([http://shapiro.bsd.uchicago.edu/Origin\\_of\\_New\\_Protein\\_Domains.html](http://shapiro.bsd.uchicago.edu/Origin_of_New_Protein_Domains.html)). New coding sequences also form by reverse transcription of processed RNAs and genome insertion of the cDNAs, sometimes producing chimeric fusions with existing exons ([http://shapiro.bsd.uchicago.edu/Table5B.Reports\\_of\\_retrogenes\\_in\\_plant\\_and\\_animal\\_genomes.html](http://shapiro.bsd.uchicago.edu/Table5B.Reports_of_retrogenes_in_plant_and_animal_genomes.html)) (Long, 2001; Betrán et al., 2002; Fu et al., 2010).

It is now clear that mobile genetic elements play a key role in establishing and rewiring genomic networks (<http://shapiro.bsd.uchicago.edu/Table5C-1.MobileElementsFoundtoBeExaptedAscis-RegulatoryControlSitesinAnimals.html>) (Feschotte, 2008; Lindblad-Toh et al., 2011; Lowe et al., 2011; Testori et al., 2012; Kokosar and Kordis, 2013). Moreover, mobile element proliferation is a key factor in the formation of very large genomes ([http://shapiro.bsd.uchicago.edu/Genome\\_Size.html](http://shapiro.bsd.uchicago.edu/Genome_Size.html)).

The potential functional importance of distributed mobile DNA in genomes grows rapidly as evidence accumulates for pervasive genome transcription (<http://shapiro.bsd.uchicago.edu/PervasiveGenomeTranscription.html>) and for the regulatory role of non-coding RNAs (ncRNAs) in genome expression, including the functional juxtaposition of distant genome regions to activate transcription (<http://shapiro.bsd.uchicago.edu/NonCodingRNAinGenomeExpression.html>). Mobile elements participate in this long-range genomic communication and provide the sequences of many ncRNAs (Kapusta et al., 2013).

## CELLS USE RNA-TARGETED EPIGENETIC CONTROL TO INHIBIT THE ACTIVITY OF MOBILE DNA

Given the high content of mobile DNA in many genomes, an important question is: what prevents all the mobility systems from destroying genome integrity? In eukaryotic cells, a major control mechanism is sncRNA-directed epigenetic formatting into silent chromatin (Law and Jacobsen, 2010; Castel and Martienssen, 2013).

Both prokaryotes and eukaryotes have systems for capturing fragments from invading DNA molecules and placing the fragments into special loci encoding sncRNAs (Dumesic and Madhani, 2014). In prokaryotes, these loci are called CRISPRs (clustered regular interspersed palindromic repeats) (<http://shapiro.bsd.uchicago.edu/CRISPRs.html>) (Marraffini and Sontheimer, 2010; Garrett et al., 2011; Bikard and Marraffini, 2013; Watanabe et al., 2013). The RNA transcripts from CRISPRs are processed into sncRNAs that target cleavage of homologous invading DNA and also inactivation of complementary mRNA (Djordjevic et al., 2012). The details of the RNA processing and interference activities are well-characterized, but the acquisition of DNA fragments is poorly understood. The process must be very rapid, because viral infection yields cells that survive the initial infection with appropriate fragments added to their CRISPR repertoire (Barrangou et al., 2007).

Virtually all eukaryotes investigated, with the notable exception of budding yeast, have mechanisms for sncRNA-directed chromatin silencing. They are based on members of the Argonaute family of sncRNA-processing proteins (<http://shapiro.bsd.uchicago.edu/microRNA-directedchromatinsilencing.html>). Plants and animals have independently evolved distinct mechanisms of processing the sncRNAs for the Argonaute family systems, but both groups use targeted epigenetic regulatory processes to defend against virus infection (Ding and Voinnet, 2007; Csorba et al., 2009) and prevent genome instability (Table 1). Like prokaryotes, *Drosophila* has specific genomic loci where it acquires fragments of invading DNA to encode the targeting sncRNAs (Brennecke et al., 2007, 2008; Handler et al., 2013).

## LIFE HISTORY EVENTS DESTABILIZE GENOMES AND ACTIVATE MOBILE DNA

Anyone who has studied real-time genome changes quantitatively knows that mutation frequencies depend upon the treatment of the experimental organism prior to measurement. A wide variety of life history events influence the natural genetic engineering (NGE) functions that generate mutations, especially mobile elements (Table 2; Shapiro, 2011). In some cases, the genome instabilities are large scale and last multiple cell or organismal generations.

Many observations demonstrate responses of the circuits controlling NGE functions to biological and abiotic inputs. It is particularly significant that many such responses occur following exceptional cell interactions with viruses or with other cells, either by infection or by hybridization (Table 2). As we might expect, the introduction of alien DNA or chromatin into a cell often has disruptive effects on genome homeostasis (Shapiro, 2014).

**Table 1 | Genome immunity by sncRNA targeting of mobile DNA (see also <http://shapiro.bsd.uchicago.edu/Table11.9.shtml> for earlier references).**

Organisms	sncRNA targets	References
Plants	Transposable elements	Rigal and Mathieu, 2011; Ng et al., 2012; Nuthikattu et al., 2013
<i>Arabidopsis</i>	Retrotransposons	Mirouze et al., 2009; Slotkin, 2010
Rice	Retrotransposons	Tian et al., 2011
<i>Brassica</i>	Retrotransposons	Zhang et al., 2013
<i>Arabidopsis</i>	Transposable elements	Mccue et al., 2012
Maize	Transposable elements	Barber et al., 2012; He et al., 2013
Plants	Viruses and viroids	Navarro et al., 2009; Pantaleo, 2011; Zhu and Guo, 2012; Ramesh et al., 2014
Rice, tobacco and <i>Laodelphgax striatellus</i> insect vector	Rice stripe virus	Xu et al., 2012b
<i>Arabidopsis</i>	Geminiviruses	Vanitharani et al., 2005; Raja et al., 2014
<i>Caenorhabditis elegans</i> germ-line	Transposons	Sijen and Plasterk, 2003; Buckley et al., 2012; Lee et al., 2012
<i>Drosophila</i>	Viruses	Van Rij et al., 2006
<i>Drosophila</i> somatic cells	Retrotransposons	Kawamura et al., 2008
<i>Drosophila</i> male germ-line	Retrotransposons	Kalmykova et al., 2005
<i>Drosophila</i> female germ-line	Transposons, retrotransposons and retroviruses	Brennecke et al., 2007, 2008
<i>Drosophila</i> female germ-line	Telomeric retrotransposons	Shpiz et al., 2009
<i>Drosophila</i> gonads	Transposons	Sienski et al., 2012
<i>Drosophila</i> somatic and germ-line cells	Transposons, retrotransposons and retroviruses	Handler et al., 2013
<i>Drosophila</i> tissue culture cells	Transposons	Chung et al., 2008
Shrimp	White spot syndrome DNA virus	Huang and Zhang, 2013; Sabin and Cherry, 2013
Mammalian cells	EMCV and NoV RNA viruses	Maillard et al., 2013
Human tissue culture cells	LINE retrotransposons	Yang and Kazazian, 2006

## EPIGENETIC CHANGES IN RESPONSE TO LIFE HISTORY EVENTS

One of the most active research areas in the second decade of the 21st century is analyzing the impact of life history events on the epigenetic layers of cell regulatory architecture (Table 3) (Chinnusamy and Zhu, 2009a; Vandegehuchte and Janssen,

**Table 2 | Life history events that lead to genome destabilization (see also <http://shapiro.bsd.uchicago.edu/TableII.8.shtml> for earlier references).**

Organism	Life history event	Genome instability	References
Plant	Polyploidization	Transposon and retrotransposon activation	Bento et al., 2013
Rice	Introgression from wild rice ( <i>Zizania</i> )	Genome-wide variation of all kinds, including transposon reactivation and transgenerational mobile element activation	Wang et al., 2009, 2010, 2013b
Apple	Polyploidization	Aneuploidy	Considine et al., 2012
<i>Brassica</i>	Intertribal hybridization; genome triplication; allopolyploidization	Retrotransposition; loss of tandem arrays; Homoeologous shuffling and chromosome compensation	Xiong et al., 2011; Fang et al., 2012; Zhang et al., 2013
Wheat, rye	Allopolyploidization	Loss of repetitive and non-coding DNA, including chromosome-specific sequences; rearrangement of syntenic blocks; transposon and retrotransposon activity	Bento et al., 2008, 2010, 2013; Kraitshtein et al., 2010; Yaakov and Kashkush, 2011b, 2012; Feldman and Levy, 2012; Tomas et al., 2012; Luo et al., 2012; Martis et al., 2013
Sunflower	Polyploidization	Chromosome rearrangements	Lim et al., 2008; Chester et al., 2012
Plants	Polyploidization	Rapid genome reshuffling	Tayale and Parisod, 2013
Plants	Polyploidization	Meiotic and fertilization abnormalities	Grandont et al., 2013
Animals	Polyploidization	Meiotic and fertilization abnormalities	Bogart and Bi, 2013; Choleva and Janko, 2013; Stenberg and Saura, 2013
<i>Squalius alburnoides</i> (Cyprinid fish)	Polyploidization	Rapid genome reshuffling; mobile element activity	Collares-Pereira et al., 2013
<i>Arabidopsis</i>	Oilseed rape mosaic virus infection	Increased homologous recombination	Yao et al., 2013
<i>Arabidopsis</i>	Heat shock	Transgenerational ONSEN retrotransposon activation	Matsunaga et al., 2012
<i>Arabidopsis</i>	Volatiles from UV-irradiated <i>Arabidopsis</i> or tobacco plants	Increased homologous recombination	Yao et al., 2011
<i>Arabidopsis</i>	Abiotic stresses (ionizing radiation, heavy metals, chlorine, temperature and water)	Somatic and heritable changes in homologous recombination, strand breakage	Boyko et al., 2010; Rahavi et al., 2011; Yao and Kovalchuk, 2011
Tobacco	Tobacco mosaic virus infection	Increased homologous recombination	Kathiria et al., 2010
Rice	Tissue culture cultivation	Genomic DNA fragment length polymorphisms	Wang et al., 2013a
Rice	Etoposide exposure	Increased transposon activity	Yang et al., 2012
Human	Human papillomavirus (HPV) integration	Extensive rearrangements, often focused on insertion site	Korzeniewski et al., 2011; Akagi et al., 2014

2013). The observed epigenetic responses include alterations to cytosine methylation in DNA (Chinnusamy and Zhu, 2009b), histone modifications in nucleosomes, and sncRNAs (Ruiz-Ferrer and Voinnet, 2009; Ng et al., 2012) as well as transgenerational inheritance of complex novel phenotypes (Zucchi et al., 2012), frequently induced by stress (Boyko and Kovalchuk, 2010). The phenomenon of hybrid vigor, or heterosis, increasingly is viewed as an alteration in sncRNA-targeted epigenetic formatting stimulated by the encounter of two distinct genome control regimes (Groszmann et al., 2011; Miller et al., 2012; Shivaprasad et al., 2012).

Many of the studies demonstrating induced epigenetic modifications also document accompanying genome instabilities and emphasize their evolutionary potential (Madlung and Wendel, 2013). It is noteworthy that many of the same stimuli are involved in both genomic and epigenomic responses in plants (Hegarty et al., 2013) and animals (Arkhipova and Rodriguez, 2013). The common stimuli include infection and symbiosis (Hamon and

Cossart, 2008; Bierne et al., 2012; Takahashi, 2014), hybridization and changes in ploidy.

## DIRECT INTERACTIONS BETWEEN NGE ACTIVITIES AND EPIGENETIC REGULATORY FUNCTIONS

In addition to disruption of sncRNA-targeted inhibition, there is limited but growing evidence that NGE functions acting on DNA molecules interact directly with epigenetic control factors. There is convincing evidence of the connection between NGE and the epigenome in DNA damage repair and retroviral or retrotransposon insertions into chromosomes.

## EPIGENETIC INVOLVEMENT IN DNA PROOFREADING AND REPAIR

There are recent reports that a specific histone modification (H3K36me3) primes DNA mismatch repair (Schmidt and Jackson, 2013), that H3K56 acetylation affects mismatch repair (Kadyrova et al., 2013), that hypoacetylation of H3K56 by HDACs 1 and 2 facilitates recruitment of non-homologous end-joining

**Table 3 | Life history events that induce epigenetic changes (see also <http://shapiro.bsd.uchicago.edu/Tablell.10.shtml> for earlier references).**

Organism	Life history event	Epigenetic change	References
Plants	Hybridization, polyploidization	sncRNA changes	Ng et al., 2012
Maize	Hybridization	rasRNA variation	Barber et al., 2012
Cotton	Allotetraploidization	Changes in mi- and siRNA content and levels	Pang et al., 2009
<i>Brassica napus</i>	Intertribal hybridization and introgression	Changes in cytosine methylation	Zhang et al., 2013
Wheat	Allopolyploidization	Multigenerational transposon methylation changes	Kraitshtein et al., 2010; Yaakov and Kashkush, 2011a,b
Wheat	Hybridization and polyploidization	Deregulation of sncRNAs	Kenan-Eichler et al., 2011
<i>Solanaceae</i>	Interspecific grafting	DNA methylation changes	Wu et al., 2013
Tobacco	Geminivirus and geminivirus-beta satellite infection	Suppression of DNA methylation-base silencing	Vanitharani et al., 2005; Buchmann et al., 2009; Yang et al., 2011
Tobacco	Tobacco mosaic virus infection	Heritable resistance to viral, bacterial and fungal pathogens	Kathiria et al., 2010
Rice	Drought exposure	Multigenerational DNA methylation changes	Zheng et al., 2013
Rice	Nitrogen deprivation	Heritable stress tolerance	Kou et al., 2011
Rice	Tissue culture cultivation	DNA methylation changes	Fukai et al., 2010; Wang et al., 2013a
Rice	Etoposide exposure	Multigenerational DNA methylation changes	Yang et al., 2012
Rice	Salt exposure	DNA methylation changes	Karan et al., 2012
Rice	Heavy metal exposure	Multigenerational DNA methylation changes	Ou et al., 2012
Rice	Abiotic stresses	Novel sncRNAs in the inflorescences	Barrera-Figueroa et al., 2012
Pear seeds	Desiccation	DNA methylation changes	Michalak et al., 2013
<i>Arabidopsis</i>	Interspecific hybridization	Polycomb response complex changes	Burkart-Waco et al., 2013
<i>Arabidopsis</i>	Geminivirus (Cabbage leaf curl virus, CaLCuV) infection	Epigenetic silencing	Aregger et al., 2012
<i>Arabidopsis</i>	Stress response	Alteration of <i>Athila</i> family retrotransposon sncRNA	Mccue et al., 2012
<i>Arabidopsis</i>	Biotic stresses (bacteria, hormones)	Increased DNA methylation	Downen et al., 2012
<i>Arabidopsis</i>	$\beta$ -amino-butyric acid	Imprinted resistance (multigenerational) to <i>Pseudomonas syringae</i> and <i>Hyaloperonospora arabidopsidis</i> fungus	Slaughter et al., 2012
<i>Arabidopsis</i>	Salt exposure	DNA methylation, nucleosome composition	Bilichak et al., 2012
<i>Arabidopsis</i>	Hyperosmotic priming	Shortening and fractionation of H3K27me3 islands	Sani et al., 2013
Wild rye	Abiotic stresses	DNA methylation	Yu et al., 2013b
Neptune grass	Cadmium	DNA methylation and chromatin patterning	Greco et al., 2012
Plant and mammalian cells	Cadmium	DNA methylation and histone modification	Wang et al., 2012
Nematode ( <i>Caenorhabditis elegans</i> )	Flock house virus expression	Transgenerational resistance transmitted by sncRNAs	Rechavi et al., 2011
Mosquito ( <i>Aedes aegypti</i> )	<i>Wolbachia</i> infection	Disruption of cytosine methylation	Ye et al., 2013
Carp	Allotetraploidization	Localized hypermethylation	Xiao et al., 2013
<i>Squalius alburnoides</i> (fish)	Polyploidization	Alterations in sncRNA patterns	Inacio et al., 2012
Rats	Exposure to dioxin and endocrine disruptors of F0 generation	Transgenerational inheritance of adult onset diseases and sperm epimutations	Manikkam et al., 2012, 2013
Rats	Vinclozolin fungicide exposure of F0 males	Transgeneration changes to physiology, behavior, metabolic activity, and transcriptome in discrete brain nuclei, altered restraint stress responses	Crews et al., 2012
Pigs	Diet supplementation of F0 with methylating micronutrients	Transgenerational inheritance of extra fat and DNA methylation changes	Braunschweig et al., 2012
Mouse neuronal cells	Short-term hypoxia	DNA methylation changes	Hartley et al., 2013
Humans	High fat diet	DNA methylation changes	Jacobsen et al., 2012
Humans	Early life trauma	DNA methylation changes	Labonte et al., 2012

(Continued)



Table 3 | Continued

Organism	Life History Event	Epigenetic change	References
Humans	Cadmium	DNA hypo-methylation	Hossain et al., 2012
Human lymphocytes	Epstein-Bar virus (EBV) infection	Hypermethylation of tumor suppressor loci, DNA methylation changes	Leonard et al., 2011; Kaneda et al., 2012; Queen et al., 2013
Human liver cells	Hepatitis B virus infection	DNA methylation, histone and sncRNA changes	Tian et al., 2013; Rongrui et al., 2014
Gastric epithelium	<i>Helicobacter pylori</i> infection	DNA methylation and histone changes	Ding et al., 2010; Alvarez et al., 2013; Chiariotti et al., 2013
Schwann cells	<i>Mycobacterium leprae</i> infection	Reprogramming to stem cell-like state	Masaki et al., 2013

(NHEJ) proteins (Miller et al., 2010; Munoz-Galvan et al., 2013), and that nucleosome remodeling is integral to DS break repair (Seeber et al., 2013). Longstanding observations document the involvement of a specific histone, gamma-H2AX, in DS break repair and NHEJ (Kinner et al., 2008; Altaf et al., 2009; Dickey et al., 2009b; Redon et al., 2009; Firsanov et al., 2011; Chen et al., 2013). A direct role in chromatin remodeling for DNA repair has been claimed for another H2 analog, H2A.Z (Xu et al., 2012a).

Published reports indicate that H2AX incorporation into chromatin suppresses conversion of single-strand nicks to DS breaks (Franco et al., 2006) and affects the processing of the ends of broken DNA molecules (Helmink et al., 2011). H2AX operates in phosphorylated form (Rogakou et al., 1998; Kinner et al., 2008).

Beyond the role of H2AX, chromatin dynamics play an essential role in DNA repair and genome homeostasis (Lahue and Frizzell, 2012; Shi and Oberdoerffer, 2012). Many reports claim repair roles for chromatin regulators, remodeling complexes and nucleosome exchange factors (Ryan and Owen-Hughes, 2011):

- in DNA damage tolerance (Conaway and Conaway, 2009; Falbo et al., 2009);
- after exposure to ionizing radiation (Hunt et al., 2013);
- in UV damage responses (Palomera-Sanchez and Zurita, 2011; Yu et al., 2011);
- in DS break repair by NHEJ and HR (Van Attikum and Gasser, 2005; Williams et al., 2007; Robert et al., 2011; Xu and Price, 2011; Price and D'andrea, 2013);
- in PolyADP-dependent DNA repair (Ahel et al., 2009);
- in NER as well as DS break repair (Osley et al., 2007; Czaja et al., 2012; Yu et al., 2013a).

Nucleosome disassembly is probably necessary for certain repair processes (Linger and Tyler, 2007; Amouroux et al., 2010; Gospodinov and Herceg, 2013), and histone modifications affect damage-induced checkpoint signaling (Chen and Tyler, 2008). Once repair is complete, nucleosome modifications are reversed, and H2AX~P is eliminated from chromatin (Svetlova et al., 2010). So-called “bystander” cells, which are not subjected to DNA damage but are in the same culture as irradiated cells, also display H2AX phosphorylation (Sokolov et al., 2007; Dickey et al., 2009a, 2011).

A key feature of genome repair is that H2AX-marked damaged DNA mobilizes to subnuclear “repair centers” where homologous recombination and NHEJ proteins also localize (Lisby and Rothstein, 2005; Plate et al., 2008; Bekker-Jensen and Mailand, 2010). A role for chromatin in mobilization of damaged DNA has been proposed (Seeber et al., 2013), but multiple sources of evidence are lacking.

#### RETROVIRAL AND RETROTRANSPOSON INTEGRASES

A more extensive case for NGE-chromatin interactions comes from analysis of retroviral and retrotransposon insertion specificities (Zhang and Mager, 2012). Each type of retrovirus displays a characteristic insertion specificity for its provirus (Lewinski et al., 2006). A number of targeting mechanisms involve epigenetic formatting molecules.

In budding yeast, Ty1 retrotransposon integrase contacts an H2A/H2B interface upstream of RNA polymerase III initiation sites (Baller et al., 2012; Bridier-Nahmias and Lesage, 2012; Mularoni et al., 2012). Histone deacetylase Hos2 and Trithorax group protein Set3 stimulate this nucleosome-targeted integration (Mou et al., 2006), and chromatin remodeling factor Isw2p is also implicated (Bachman et al., 2005). In contrast, the Ty5 retrotransposon inserts in silent chromatin, targeted by binding of its integrase to the Sir4 heterochromatin nucleating factor (Xie et al., 2001; Dai et al., 2007; Brady et al., 2008; Baller et al., 2011).

HIV and other lentiviral targeted integration into actively transcribed regions of the genome is associated with transcription-associated histone modifications, including H3 acetylation, H4 acetylation, and H3 K4 methylation, but is disfavored in regions rich in transcription-inhibiting modifications, which include H3K27me3 and DNA CpG methylation (Wang et al., 2007). The specificity results from integrase tethering by the LEDGF/p75 chromatin-binding growth factor (Vanegas et al., 2005; Llano et al., 2006; Ciuffi, 2008; Meehan and Poeschla, 2010; Zheng et al., 2010; Christ and Debyser, 2013). Replacing the LEDGF/p75 domain that interacts with expressed chromatin by the CBX1 domain, which binds histones H3K9me2 or H3K9me3 found in pericentric heterochromatin, targets HIV insertions to silent chromatin regions (Gijsbers et al., 2010).

Murine leukemia virus (MuLV) insertion targeting to initiation sites upstream of actively transcribed regions involves integrase interactions with bromodomain proteins BRD2, BRD3, and BRD4 (De Rijck et al., 2013; Gupta et al., 2013; Sharma et al., 2013a). Interestingly, chromatin recognition bromodomain

protein BRD4 antagonizes HIV provirus reactivation (Zhu et al., 2012).

Certain retrotransposons are specifically targeted to centromeres (Wolfgruber et al., 2009; Birchler and Presting, 2012; Tsukahara et al., 2012; Sharma et al., 2013b), which have a special chromatin configuration characterized by centromeric versions of H3 (Henikoff and Dalal, 2005; Vos et al., 2006; Partridge, 2008; Zhang et al., 2008a). Centromeric retrotransposons in rice are highly associated with H3K9me2, a hallmark for heterochromatin (Neumann et al., 2007). Some centromeric retrotransposons encode integrase proteins with histone-binding chromodomains at their carboxy-termini (Neumann et al., 2011). Chromodomains recognize lysine methylation (Blus et al., 2011; Yap and Zhou, 2011; Eissenberg, 2012).

It is probably not coincidental that the most widely distributed group of retrotransposons among all eukaryotic clades are the “chromoviruses,” which are so named because they have chromodomains in their integrase proteins (Gorinsek et al., 2004; Kordis, 2005; Novikov et al., 2012; Weber et al., 2013). A chromodomain has been reported to target fungal chromovirus MAGGY insertions to heterochromatin marked by H3K9me2/me3 (Gao et al., 2008). An integrase chromodomain also participates in activator protein-targeted insertion of fission yeast retrotransposon Tfl upstream of RNA polymerase II transcription start sites (Hizi and Levin, 2005; Chatterjee et al., 2009).

## DNA TRANSPOSONS

In contrast with many retrotransposons that interact with nucleosomes, the DNA transposon Hermes inserts preferentially in budding yeast into nucleosome-free regions of the genome (Gangadharan et al., 2010). The widely used P element DNA transposons in *Drosophila* show targeting (called “P element homing”) by incorporating binding sites for various regulatory factors, including chromatin insulators (Bender and Hudson, 2000; Fujioka et al., 2009) and Polycomb group response elements (Kassis, 2002; Cheng et al., 2012).

## EPIGENETIC REFORMATTING AFTER DNA REPLICATION AND ncRNAs AS POTENTIAL AGENTS FOR TRANSMITTING EXPERIENCE TO THE GENOME

While the evidence is increasingly abundant for effects of different life history events on epigenetic regulation in general, and on genome homeostasis in particular, it is far from clear how those effects occur (Lim and Brunet, 2013). We know very little about the connections between cell sensors and epigenetic (re)formatting complexes (Erdel et al., 2011; Narlikar et al., 2013). Deciphering those connections is currently an important research goal.

DNA replication provides a key decision point for maintaining or changing chromatin configurations (Poot et al., 2005; Liu and Gong, 2011; Mermoud et al., 2011). The replication apparatus must disassemble chromatin for polymerization and then reassemble chromatin once replication is complete. Replication takes place only in dividing cells, and transgenerational inheritance of epigenetic states must involve the proliferating cells that give rise to gametes. Transfer of outside information from somatic

tissues to the germline has been reported in mammals (Sharma, 2013; Skinner et al., 2013). And epigenetic windows of susceptibility to environmental insults have been suggested during sperm development (Soubry et al., 2014). Since there is no segregated germ line in plants and eukaryotic microbes, the same cells that experience environmental inputs can also be the progenitors of gametes.

A number of different factors have been found or hypothesized to participate in post-replication chromatin restoration: histone chaperones (Budhavarapu et al., 2013), RNA editing and sncRNAs (Savva et al., 2013), chromatin remodeler SMARCD1 (Mermoud et al., 2011), chromatin assembly factor 1 (Huang and Jiao, 2012), histone chaperon FACT (Winkler and Luger, 2011) and Swi/Snf complexes (Neves-Costa and Varga-Weisz, 2006; Ryan and Owen-Hughes, 2011; Zhu et al., 2013), and ISW1 complexes (Erdel and Rippe, 2011).

One frequently overlooked feature of post-replication reestablishment of epigenetic formatting is where in the nucleus it might occur. Replication takes place in specialized “replication factories” (Vago et al., 2009; Guillou et al., 2010). Does chromatin reestablishment occur in the same location or does it involve migration of newly replicated DNA segments to distinct subnuclear “chromatin factories,” like the ones that exist in the nucleolus for heterochromatin formation on rRNA-encoding DNA (Guettg and Santoro, 2012)? If so, such post-replication relocation would be guided by the nucleoskeleton and lncRNAs (Mercer and Mattick, 2013; Mercer et al., 2013) and might present an attractive target for stress response and sensory input signaling (Weiner et al., 2012).

It is notable that changes to ncRNAs are frequently cited with regard to the impact of life history events on the genome (Sunkar et al., 2007; Khraiweh et al., 2012; Lelandais-Briere et al., 2012; Nakaminami et al., 2012; Amaral et al., 2013). In the plant literature, there is documentation of numerous ncRNA changes in response to particular biotic and abiotic stress regimes (Table 4).

A number of observations about resistance to biotic and abiotic stresses are consistent with a key role for ncRNA changes in life history responses. Several viruses encode siRNA suppressors to overcome host defenses (Jiang et al., 2012; Omarov and Scholthof, 2012; Guo and Lu, 2013). Transgenic constructs encoding constitutive miRNA expression can lead to salt and drought tolerance in creeping bentgrass (Zhou et al., 2013), to immunity against blast fungus in rice (Li et al., 2014), and in *Arabidopsis* to greater salt and alkalinity sensitivity (Gao et al., 2011). Acquired aphid resistance in *Arabidopsis* involves sncRNA changes (Kettles et al., 2013), and most acquired stress resistances in plants display transgenerational epigenetic inheritance (Holeski et al., 2012; Luna and Ton, 2012; Slaughter et al., 2012).

## SPECULATIVE CONCLUSIONS ABOUT AN EPIGENETIC INTERFACE BETWEEN EXPERIENCE AND GENOME CHANGE

Mobile DNA and other NGE functions are the key agents for adaptively significant changes in genome organization and DNA sequences. The data reviewed and tabulated above establish the importance of RNA-directed chromatin formatting in the regulation and operation of mobile elements, viruses and DNA repair

**Table 4 | Changes in non-coding RNAs in response to life history events.**

Stress or input	Organism(s)	References
Salt	Multiple plants	Ding et al., 2009; Qin et al., 2011; Macovei and Tuteja, 2012; Carnavale Bottino et al., 2013; Li et al., 2013; Ren et al., 2013; Zhuang et al., 2014
Drought	Multiple plants	Barrera-Figueroa et al., 2011; Li et al., 2011a; Qin et al., 2011; Wang et al., 2011; Eldem et al., 2012; Ferreira et al., 2012; Ding et al., 2013; Gentile et al., 2013; Shuai et al., 2013
Waterlogging	Maize, poplar	Zhang et al., 2008b; Liu et al., 2012; Ren et al., 2012; Zhai et al., 2013
Cold stress	Wheat	Tang et al., 2012
Aluminum	Soybeans	Chen et al., 2012a; Zeng et al., 2012
Cadmium	Radish	Xu et al., 2013
Boron	Barley	Ozhuner et al., 2013
ethylene	<i>Medicago truncatula</i> (barrel clover)	Chen et al., 2012b
Ozone	<i>Arabidopsis</i>	Iyer et al., 2012
Hypoxia	<i>Arabidopsis</i>	Moldovan et al., 2010
Low phosphorous	Maize	Zhang et al., 2012
Low nitrate	Maize	Xu et al., 2011
Sulfur deprivation	<i>Chlamydomonas reinhardtii</i>	Shu and Hu, 2012
Abiotic stresses	Multiple plants	Kulcheski et al., 2011; Li et al., 2011b; Barrera-Figueroa et al., 2012; Sun et al., 2012; Zhan et al., 2012; Ballen-Taborda et al., 2013
Physiological stressors and invasive plant infection	Rice blast fungus, <i>Magnaporthe oryzae</i>	Raman et al., 2013
Virus infection	Multiple plants, rice	Du et al., 2011; Sha et al., 2014
Viral and bacterial infections	Multiple plants, cassava ( <i>Xanthomonas</i> infection)	Perez-Quintero et al., 2012; Zvereva and Pooggin, 2012; Pelaez and Sanchez, 2013; Quintero et al., 2013
Bacterial/phytoplasma infection	Multiple plants, lime trees	Zhang et al., 2011; Ehya et al., 2013
Powdery mildew infection	Wheat	(Xin et al., 2011) miRNAs (Xin et al., 2010)
<i>Verticillium</i> wilt infection	Cotton, eggplant	Yin et al., 2012; Yang et al., 2013

functions. In addition, there is a remarkable correlation between the life history events that activate NGE functions to destabilize genomes and those that lead to alteration of chromatin states and DNA methylation patterns.

The preceding observations lead to the plausible hypothesis that epigenetic regulation serves as a key interface between organismal life history and the agents that restructure genomic DNA. This hypothesis is supported by the limited number of cases where empirical observations have established direct molecular connections between NGE functions and components of the epigenetic control system: histones, nucleosomes, and chromatin reformatting complexes.

If, as I expect, further research bolsters the epigenome-NGE correlations and connections documented above, then we need to ask: what component(s) of the epigenetic control apparatus communicate information about experience to NGE operators? We do not know the answer to this fundamental question. However, the data reported in **Table 4** indicate that ncRNAs are good candidates for key intermediates in the experience-genome signal transduction process. If this is so, then ncRNAs are logical molecular targets for modulating genome change toward potentially adaptive outcomes. Let us hope that research aimed at examining this proposal deepens our understanding of how life history impacts both epigenetic and genome change operations (**Tables 2–4**), whether or not my speculation ultimately proves to be correct.

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